Attorney Docket No. 9362-3 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Williams *et al.*
Serial No.: 10/662,757
Filed: September 15, 2003
Confirmation No.: 1920
Group Art Unit: 1792
Examiner: James Lin

For: *INTRALUMINAL PROSTHESES AND CARBON DIOXIDE-ASSISTED METHODS OF IMPREGNATING SAME WITH PHARMACOLOGICAL AGENTS*

Date: June 30, 2008

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Commissioner for Patents
Box 1450
Alexandria, Virginia 22313-1450

APPELLANT'S BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

Sir:

This Appeal Brief is filed pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed May 6, 2008.

The Commissioner is authorized to charge Deposit Account No. 50-0220 in the amount of $510.00 as the fee for filing an Appeal Brief. This amount is believed to be correct. However, the Commissioner is hereby authorized to charge any deficiency or credit any refund to Deposit Account No. 50-0220.

REAL PARTY IN INTEREST

The real party in interest is Synecor, LLC, the assignee of the rights to this application by virtue of assignment from the inventors to Synecor, LLC, recorded at the United States Patent and Trademark Office on December 17, 2003 on Reel 014795, Frame 0446.

RELATED APPEALS AND INTERFERENCES

Appellants are aware of no related appeals or interferences that would be affected by the present appeal.

STATUS OF CLAIMS

Claims 73-104 are pending in the present application as of the filing date of this Appeal Brief. As of the filing date of this Appeal Brief, Claims 73-104 stand finally rejected under 35 U.S.C. § 103(a) as noted in the Final Office Action mailed February 12, 2008 and the Advisory Action mailed April 25, 2008.

Appellants appeal the rejection of Claims 73-104. A copy of Claims 73-104 is attached hereto as **Claims Appendix,** presenting the claims at issue as twice rejected in the Final Office Action dated February 28, 2007 and the Advisory Action mailed April 25, 2008.

STATUS OF AMENDMENTS

All amendments made by Appellants during prosecution are believed to be entered as indicated by the Final Office Action dated February 12, 2008.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is directed to a method of impregnating an intraluminal prosthesis with pharmacological agents for delivery within a body of a subject. *See*, Specification, for example, at least, on page 4, lines 1-18; and Figures 1-3. Accordingly, independent **Claim 73** is directed to a method of:

immersing an intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent, wherein the intraluminal prosthesis comprises non-layered polymeric material (Fig.1, block 100);

pressurizing the mixture of carrier fluid (Fig.1, block 110) and pharmacological agent for a time sufficient to cause the carrier fluid and pharmacological agent to at least partially penetrate the non-layered polymeric material;

removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the pharmacological agent becomes elutably trapped within the non-layered polymeric material (Fig.1, block 120) in a predetermined concentration gradient, wherein the concentration gradient

defines an elution profile of the pharmacological agent from the non-layered polymeric material when the intraluminal prosthesis is deployed within a body of a subject. *See* Specification, for example, at least on page 4, lines 2-19; on page 15, lines 6-12; on page 16, line 17 through page 17, line 2; on page 18, lines 12-29; and Fig. 1.

The controlled conditions involve controlling at least one parameter in a predetermined pattern, such parameters include temperature, rate of temperature change, pressure, rate of pressure change, carrier fluid quantity, and rate of carrier fluid quantity. Specification, page 16, lines 22-28. The carrier fluid can be carbon dioxide. Specification, page 5, lines 4-25. Further, one or more portions of the intraluminal prosthesis may be masked with a protective layer of material prior to immersion in a mixture of carrier gas and pharmacological agent so as to create portions or regions of the polymeric material having different concentrations of the pharmacological agent entrapped in it, or to partition one pharmacological agent in one region of the prosthesis from another pharmacological agent in a second (or third or fourth) region of the prosthesis. *See* Specification, for example, at least on page 18, line 29 through page 19, line 1; and on page 19, lines 2-4.

Independent **Claim 88** is directed to a method of:

immersing an intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent, wherein the intraluminal prosthesis comprises non-layered polymeric material;

placing the intraluminal prosthesis within a pressure vessel (Fig. 2, block 200);

pressurizing the interior of the pressure vessel with an inert gas to a predetermined pressure (Fig. 2, block 210), wherein the inert gas is selected from the group consisting of helium, nitrogen, and argon;

supplying a mixture of a carrier fluid and a pharmacological agent into the pressure vessel (Fig. 2, block 220);

exposing the non-layered polymeric material and the mixture of carrier fluid and pharmacological agent in the pressure vessel for a time such that the carrier fluid and pharmacological agent at least partially penetrate the non-layered polymeric material (Fig. 2, block 230); and

releasing the pressure in the pressure vessel over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient (Fig. 2, block 240), wherein the concentration gradient defines an elution profile of the pharmacological agent from the non-layered polymeric material when the intraluminal prosthesis is deployed within a body of a subject. *See* Specification, for example, at least on page 4, line 19 through page 5, line 2; on page 16, line 17 through page 17, line 2; on page 18, lines 12-28; on page 19, lines 9-17; and in Fig. 2.

The controlled conditions recited in Claim 88 involve controlling at least one parameter in a predetermined pattern, such parameters include temperature, rate of temperature change, pressure, rate of pressure change, carrier fluid quantity, and rate of carrier fluid quantity. *See* Specification, for example, at least on page 16, lines 22-28.

Independent **Claim 99** is directed to a method of:

masking portions of an intraluminal prosthesis with a protective layer of material such that the intraluminal prosthesis has first and second unmasked portions, wherein the intraluminal prosthesis comprises non-layered polymeric material (*See* Specification, for example, at least on page 18, line 29 through page 19, line 1);

immersing the intraluminal prosthesis in a mixture of a carrier fluid and first and second pharmacological agents (*See* Specification, for example, at least original claim 1; Fig.6; and on page 24, lines 8-28);.

pressurizing the mixture of carrier fluid and pharmacological agents for a time sufficient to cause the carrier fluid and the first pharmacological agent to at least partially penetrate the first unmasked portion and to cause the carrier fluid and the second pharmacological agent to at least partially penetrate the second unmasked portion (*See* Specification, for example, at least on page 4, lines 9-14 and 24-32, on page 18 lines 22-29 and Fig. 2); and

removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and such that an amount of the first pharmacological agent remains elutably trapped within the first

unmasked portion in a predetermined concentration gradient and an amount of the second pharmacological agent remains elutably trapped within the second unmasked portion in a predetermined concentration gradient, wherein each concentration gradient defines an elution profile of a respective pharmacological agent from the non-layered polymeric material when the intraluminal prosthesis is deployed within a body of a subject. *See* Specification, for example, at least on page 19, lines 9-17.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether Claims 73, 74, 76, 80-84 and 86 are properly rejected under 35 U.S.C §103(a) as unpatentable over U.S. Patent Publication No. 2003/0104030 to Igaki et al.

2. Whether Claims 75, 99-101 and 104 are properly rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent Publication No. 2003/0104030 to Igaki et al. in view of U.S. Patent No. 6,251,136 to Guruwaiya.

3. Whether Claims 73,74, 76-78, 80-82, 86, 88, 89, 91-93 and 98 are properly rejected under 35 U.S.C. §103(a) as unpatentable over European Patent No. EP 0405284 to Greiner.

4. Whether Claims 75, 90 and 99-104 are properly rejected under 35 U.S.C. §103(a) as unpatentable over European Patent No. EP 0405284 to Greiner in view of U.S. Patent No. 6,251,136 to Guruwaiya.

5. Whether Claim 79 is properly rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent Publication No. 2003/0104030 to Igaki et al. in view of U.S. Patent No. 6,670,398 to Edwards.

6. Whether Claims 79 and 95 are properly rejected under 35 U.S.C. §103(a) as unpatentable over European Patent No. EP 0405284 to Greiner in view of U.S. Patent No. 6,670,398 to Edwards.

7. Whether Claims 85 and 97 are properly rejected under 35 U.S.C. §103(a) as unpatentable over European Patent No. EP 0405284 to Greiner in view of PCT Publication WO 01/87368 to Mehta.

8. Whether Claim 87 is properly rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent Publication No. 2003/0104030 to Igaki et al. in view of U.S. Patent No. 6,299,604 to Ragheb.

9. Whether Claim 87 is properly rejected under 35 U.S.C. §103(a) as unpatentable over European Patent No. EP 0405284 to Greiner in view of U.S. Patent No. 6,299,604 to Ragheb.

10. Whether Claims 81, 83, 84, 86, 93, 94, 96 and 98 are properly rejected under 35 U.S.C. §103(a) as unpatentable over European Patent No. EP 0405284 to Greiner in view of U.S. Patent Publication No. 2003/0104030 to Igaki et al.

ARGUMENT

I. 35 U.S.C. §103 Analysis

To establish a *prima facie* case of obviousness, the prior art reference or references when combined must teach or suggest all the recitations of the claims, and there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. §2143. A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v. Teleflex Inc.,* 550 U. S. 1, 15 (2007). A corollary principle is that, when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be unobvious. *Id.* at 12. If a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual

application is beyond his or her skill. *Id.* at 13. A Court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. *Id.* at 13. When it is necessary for a Court to look at interrelated teachings of multiple patents, the Court must determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *Id.* at 14.

Appellants respectfully submit that the pending independent claims are patentable over the cited references for at least the reason that the cited references do not disclose or suggest many of the recitations of the claims. The patentability of the pending claims is discussed in detail hereinafter.

II. §103 Rejections of Independent Claim 73 and Claims Dependent Therefrom are Overcome

Claims 73, 74, 76, 80-84 and 86 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent Publication No. 2003/0104030 to Igaki et al. (hereinafter "Igaki"). In addition, Claims 73, 74, 76-78, 80-82, 86 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over European Patent No. EP 0405284 to Greiner (hereinafter "Greiner"). Dependent Claim 75 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Igaki in view of U.S. Patent No. 6,251,136 to Guruwaiya (hereinafter "Guruwaiya"). In addition, dependent Claim 75 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greiner in view of Guruwaiya. Appellants respectfully request reversal of these rejections.

A. Independent Claim 73

Appellants' independent Claim 73 recites a method of impregnating an intraluminal prosthesis with a pharmacological agent, comprising:

> immersing an intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent, wherein the intraluminal prosthesis comprises non-layered polymeric material;
>
> pressurizing the mixture of carrier fluid and pharmacological agent for a time sufficient to cause the carrier fluid and pharmacological agent to at least partially penetrate the non-layered polymeric material;
>
> removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the pharmacological agent becomes elutably trapped

> within the non-layered polymeric material in a predetermined concentration gradient, wherein the concentration gradient defines an elution profile of the pharmacological agent from the non-layered polymeric material when the intraluminal prosthesis is deployed within a body of a subject.

Appellants respectfully traverse the rejection of independent Claim 73 and claims dependent therefrom. Each of the cited references is discussed below.

1. Igaki

Igaki fails to teach or suggest removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient. In fact, the Final Action mailed February 12, 2008 (hereinafter the "Action") concedes that Igaki fails to teach a drug elutably trapped within polymeric material in a predetermined concentration gradient. (Action, Page 2). However, the Action states that "Igaki teaches that the pressure is gradually exhausted (i.e., removing pressure over a predetermined period of time) in a reaction chamber (i.e., under controlled conditions) and, thus, teaches all the steps as claimed." (Action, Page 3). On this basis, the Action then concludes that, "because the method of Igaki is so similar to the claimed steps, the two methods must necessarily achieve similar results." (Action, Page 3). Appellants respectfully disagree.

Igaki does not teach the same steps nor does it achieve similar results as those of the present invention. The Action cites to paragraph 0062 of Igaki for support for the assertion that Igaki "teaches all the steps as claimed" and therefore that "the two methods must necessarily achieve the same results." Action, page 3. Paragraph 0062 of Igaki recites:

> Finally, a third valve 31 is opened to exhaust CO_2 within the reaction chamber 27 gradually to set the inside of the reaction chamber 27 open to atmosphere. The drug 26 is now **fully impregnated** in the stent 1 to complete the luminal stent according to the present invention.
> (emphasis added)

Thus, a full and fair reading of paragraph 0062 of Igaki fails to show that the steps of Igaki result in a concentration gradient in the polymeric material as taught by the present invention but rather describes a process in which a stent is "fully impregnated" with the drug." Clearly, one of

ordinary skill in the art would not reasonably interpret this to mean the formation of a predetermined concentration gradient as taught by the present invention. Further, the data presented in Table 3 and in Figures 10 and 11 of Igaki support the conclusion that the methods of Igaki in fact teach that only a single concentration of drug is impregnated in the polymeric material of Igaki. For instance, in Table 3 each example presents only a single concentration of impregnated drug. Furthermore, commenting on the Examples, Igaki states "[i]t has been shown that the quantity of transilast impregnated in the stent depends on the pressure and temperature of the supercritical fluid CO_2, and that, in particular, if the temperature at which CO_2 is made into a supercritical fluid is high, the quantity of transilast impregnated is increased." (Igaki, Para. 98). No teaching or suggestion is made of controlling such variables as pressure or temperature so as to achieve a concentration gradient in the polymeric material but rather, Igaki describes only increasing or decreasing the absolute amount of drug impregnated in the stent. Thus, based on the data and text presented in Igaki et al., one of ordinary skill in the art would not reasonably conclude that Igaki et al. teaches a concentration gradient in the polymeric material.

The statements in the Action such as "must necessarily have some sort of concentration gradient within the polymeric material in the method of Igaki" and the "concentration gradient, therefore must necessarily define an elution profile of the pharmacological agent as required in the claims," appear to be based on a conclusion that Igaki inherently teaches removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient as is taught by the present invention. Appellants respectfully submit that, as stated in the M.P.E.P., a reference cannot be relied upon for allegedly inherent teachings to support a rejection under 35 U.S.C. §103. Specifically, it is stated in § 2141.02 (V) of the M.P.E.P., with a citation to *In re Rijckaert*, that "[o]bviousness cannot be predicated on what is not known at the time an invention was made, even if the inherency of a certain feature is later established." (28 USPQ2d 1955 (Fed. Cir. 1993)).

Contrary to the assertion in the Advisory Action mailed April 25, 2008, *In re Rijckaert* does, in fact, address the issue of the use of inherency in a 35 U.S.C. §103 rejection. In that case, the court reversed the Board of Patent Appeals and Interferences (BPAI) decision to uphold an

obviousness rejection that was based on a conclusion that the relationship between time compression/expansion and the three particular variables was inherent in the prior art (28 USPQ2d at1957). The court agreed with the appellant that "the examiner's assumptions do not constitute the disclosure of prior art" and stated that "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency]." (*Id.*) The court then citing to *In re Spormann* stated "[t]hat which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." (*Id.*) Thus, the use of the Igaki reference for its allegedly inherent teachings as a necessary basis for this obviousness rejection renders the rejection improper and Appellants request that it be withdrawn for at least this reason.

Even if one assumes that using an allegedly inherent teaching as basis for an obviousness rejection is proper (which Appellants do not concede), the present rejection still fails because no extrinsic evidence is provided in the Action to make it clear that the missing descriptive matter is necessarily present as is required for such an argument. The legal standard for inherency is set forth in section 2112 in the MPEP and states that "[t]o establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." (*In re Robertson* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). (Emphasis added.) The MPEP also cites *Ex parte Levy* as stating that "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." (17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)). It is clear from these cases that in order for the standard for inherency to be met, the allegedly inherent characteristic must necessarily flow from the teachings of the cited art and such a determination must be supported by fact or technical reasoning.

In the present case, there is no teaching or suggestion in the Igaki reference that the pressure was necessarily removed over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the

pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient as is taught by the present invention. This is mere speculation on the Examiner's part and there is no fact or technical reasoning provided in support of this statement, as required to demonstrate that the methods of the claimed invention are inherently disclosed in the Igaki reference. Thus, there is no evidence that the claimed methods necessarily flow from the teachings of the cited art and therefore the claimed methods of this invention cannot be obvious as inherent in the teachings of Igaki.

Furthermore, contrary to the assertions in the Action, the only method provided in Igaki for controlling the release time point and quantity of an impregnated drug is via the use of layers of biodegradable polymer material and not via a concentration gradient. Igaki specifically states "[b]y forming a further biodegradable polymer layer on the stent surface, it becomes possible to control the release rate of the drug into the blood, impregnated inside of the stent." (Igaki, Para, 0026). Igaki also states "[b]y providing the layer(s) of the drug-containing biodegradable polymer in this manner, one or more drugs may be impregnated in the stent, and it is possible to permit more strict control of the drug releasing time point or the quantity of the released drug, or different drugs can be released at the desired same time point." (Igaki, Para. 0072). In Paragraph 0067 of Igaki it is further stated "...[f]or delaying the release of the drug impregnated in the stent into the blood vessel, it is also possible to form the layer of the biodegradable polymer material, formed only of the biodegradable polymer...." (Igaki,) Accordingly, Igaki fails to teach or suggest a method of impregnating an interluminal prosthesis comprising removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and ***the pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient***, as taught by the present invention. In fact, Appellants submit that the teachings of Igaki of the use of layers for controlling the release time point and quantity of an impregnated drug teaches away from the use of concentration gradients.

Appellants note that the Action further states that a predetermined concentration gradient can be zero. (Action, Page 3). Appellants respectfully disagree. One of skill in the art would know that the term gradient is defined as "the rate of regular or graded ascent or descent" and that a "concentration gradient" is defined as "a gradual change in the concentration of solutes in a

solution as a function of distance through a solution" (see the dictionary definitions included herein in the Evidence Appendix). A concentration can be zero; however, a gradient by definition cannot be zero. Clearly one of ordinary skill in the art would not reasonably consider a concentration gradient to be zero.

Thus, one of ordinary skill in the art would not, upon reading Igaki, produce a stent comprising a non-layered polymeric material with a drug concentration gradient in the nonlayered polymeric material as taught in the present application. To the contrary, one skilled in the art, upon reading Igaki, would use various layers to accomplish what Appellants accomplish via a concentration gradient. The fact that Igaki utilizes layers to control the time of drug release and the quantity of drug release illustrates that Igaki does not utilize or appreciate utilizing a drug concentration gradient for accomplishing time of drug release and/or quantity of drug release.

Accordingly, Igaki fails to teach or suggest all of the recitations of independent Claim 73 and Appellants respectfully request withdrawal of this rejection.

2. Greiner

Greiner describes a method of impregnating a catheter, made of polymeric material, with a pharmaceutical. The catheter is immersed into a saturated solution of a pharmaceutical in a solvent. The saturated solution serves as a swelling agent and swells the polymeric material of the catheter. The catheter is contacted with the swelling agent at or near supercritical pressure and temperature of the solvent. The pressure is then reduced from supercritical pressure to release the solvent from the catheter, thereby leaving the pharmaceutical impregnated within the catheter. Greiner fails to teach or suggest removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient.

The Action states that the polymeric material of Greiner would "necessarily have a concentration gradient of the pharmacological agent for substantially the same reasons as discussed..." (for Igaki). Action, Page 4. Further, the Action states once again that a concentration gradient can be zero. *Id.* Appellants respectfully disagree.

Similar to Igaki, Greiner also fails to teach or suggest an intraluminal prosthesis wherein a ***pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient*** as taught in the present application. In fact, the catheter of the Greiner invention is discussed only in terms of being impregnated with specific concentrations of a drug. Thus, Greiner states that "[t]he catheter is found to contain 25% benzocaine by weight...." (Greiner, Col. 5, Example 1). In Example 2, Greiner states that the catheter "is found to contain 42% benzocaine." Thus, Greiner provides no teaching or suggestion of a concentration **gradient** within a non-layered polymeric material as is taught by the present invention.

Further, contrary to the allegations in the Action, Greiner does not describe removing the pressure over a predetermined time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient as recited in Claim 73 of the present application. The Action cites to column 4, lines 2-6 of Greiner wherein it states "[a]fter contacting, the volatile swelling agent is separated from the catheter, leaving the pharmaceutical behind. Because of the volatility of the swelling agents employed, separation is easily accomplished by lowering the pressure." Action, Page 5. The Action then contends that "[t]here must be some control of how fast the rate of pressure changes" (*Id.*) but does not provide any evidence for such a supposition.

As discussed above, a reference cannot be relied upon for allegedly inherent teachings to support a rejection under 35 U.S.C. §103. Specifically, it is stated in § 2141.02 (V) of the M.P.E.P., with a citation to *In re Rijckaert*, that "[o]bviousness cannot be predicated on what is not known at the time an invention was made, even if the inherency of a certain feature is later established." (28 USPQ2d 1955 (Fed. Cir. 1993)). Furthermore, even if one assumes that using an allegedly inherent teaching as basis for an obviousness rejection is proper (which Appellants do not concede), the present rejection still fails because, as pointed out above, no extrinsic evidence is provided in the Action to make it clear that the missing descriptive matter is necessarily present in Greiner as is required for such an argument.

As stated in the Manual for Patent Examining Procedure § 2112 (V) when an examiner relies upon a theory of inherency, "the examiner must provide a basis in fact and/or technical

reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990). Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." Ex parte Skinner, 2USPQ2d 1788, 1789 (Bd. Pat. App. & Int. 1986). Also, the examiner has the initial burden of providing such evidence or technical reasoning. See In re Spada, 911 F.2d 705, 708, 15 USPQ2d. 1655, 1657 (Fed. Cir. 1990); In re King, 801 F.2d 1324. 1327, 231 USPQ 136, 138-139 (Fed. Cir. 1986). In the present rejection, no such basis in fact and/or technical reasoning has been provided to reasonably support the allegation that Greiner inherently describes removing the pressure over a predetermined time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient as recited in Claim 73 of the present application.

In view of the foregoing, Appellants respectfully submit that the rejections under 35 U.S.C. §103(a) of independent Claim 73 and claims dependent thereon over Igaki and/or Greiner are overcome and request that these rejections be withdrawn.

B. Dependent Claim 75

Claim 75 depends from independent Claim 73 and recites the method of Claim 37,

> further comprising masking one or more portions of the intraluminal prosthesis with a protective layer of material prior to immersing the intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent, wherein the protective layer of material is configured such that the mixture of carrier fluid and pharmacological agent at least partially penetrate only unmasked portions of the non-layered polymeric material during the pressurizing step..

Igaki, Greiner and Guruwaiya

As discussed above, Igaki and Greiner fail to teach or suggest all of the recitations of independent Claim 73. Further, Guruwaiya fails to remedy the deficiencies of Igaki and/or Greiner. Guruwaiya simply discusses the use of known masking techniques. Therefore, Igaki, Greiner and Guruwaiya, alone or in any combination, fail to teach or suggest all of the recitations of independent Claim 73 and dependent claim 75 so as to provide a motivation or reasonable

expectation of success that would lead one of ordinary skill in the art, at the time this invention was made, to carry out the methods of the claimed invention. Accordingly, Appellants respectfully request reversal of this rejection.

C. Dependent Claim 86

Claim 86 depends from independent Claim 73 and recites wherein the non-layered polymeric material is a coating on a portion of the intraluminal prosthesis.

Igaki and Greiner

As discussed above, Igaki and Greiner fail to teach or suggest all of the recitations of independent Claim 73. With regard to dependent Claim 86, the Action states that the polymeric material can be formed only on the surface. The Action provides no support for this assertion and none can be found in either Igaki and Greiner. At most, Igaki discusses a <u>further</u> layer of polymeric material on the surface of the impregnated stent in order to control the rate of release of the drug impregnated in the stent. (Igaki, *see, e.g.,* Abstract, para. 0017-0027). Greiner describes a method of impregnating a catheter, made of polymeric material, with a pharmaceutical. The catheter is immersed into a saturated solution of a pharmaceutical in a solvent. The saturated solution serves as a swelling agent and swells the polymeric material of the catheter. The catheter is contacted with the swelling agent at or near supercritical pressure and temperature of the solvent. The pressure is then reduced from supercritical pressure to release the solvent from the catheter, thereby leaving the pharmaceutical impregnated within the catheter. Thus, there is no teaching or suggestion in either Igaki or Greiner that the polymeric material is a coating on a portion of the intraluminal prosthesis as recited in Claim 86 of the present invention.

Accordingly, dependent Claim 86 is independently patentable over Igaki and/or Greiner and Appellants respectfully request withdrawal of these rejections.

III. <u>§103 Rejection of Claim 88 and Claims Dependent Therefrom are Overcome</u>

Claims 88, 89, 91-93 and 98 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greiner. In addition, dependent Claim 90 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greiner in view of Guruwaiya.

A. Independent Claim 88

Appellants' independent Claim 88 recites a method of impregnating an intraluminal prosthesis with a pharmacological agent, comprising:

> immersing an intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent, wherein the intraluminal prosthesis comprises non-layered polymeric material;
>
> placing the intraluminal prosthesis within a pressure vessel;
>
> pressurizing the interior of the pressure vessel with an inert gas to a predetermined pressure, wherein the inert gas is selected from the group consisting of helium, nitrogen, and argon;
>
> supplying a mixture of a carrier fluid and a pharmacological agent into the pressure vessel;
>
> exposing the non-layered polymeric material and the mixture of carrier fluid and pharmacological agent in the pressure vessel for a time such that the carrier fluid and pharmacological agent at least partially penetrate the non-layered polymeric material; and
>
> releasing the pressure in the pressure vessel over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient, wherein the concentration gradient defines an elution profile of the pharmacological agent from the non-layered polymeric material when the intraluminal prosthesis is deployed within a body of a subject.

Greiner

Greiner, as discussed above, fails to teach or suggest removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration as taught by the presently claimed invention. Thus, for at least the same reason that Greiner fails to teach or suggest all of the recitations of independent Claim 73, as discussed above, Greiner fails to teach or suggest all of the recitations of independent Claim 88 so as to provide a motivation or reasonable expectation of success that would lead one of ordinary skill in the art, at the time this invention was made, to carry out the methods of the claimed invention. As such, Appellants respectfully assert that the 35 U.S.C. §103 rejections of independent Claim 88 and claims depending therefrom, are overcome, and thus respectfully request their withdrawal.

B. Dependent Claim 90

Claim 90 depends from independent Claim 88 and recites the method of Claim 88,

> further comprising masking one or more portions of the intraluminal prosthesis with a protective layer of material prior to immersing the intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent, wherein the protective layer of material is configured such that the mixture of carrier fluid and pharmacological agent at least partially penetrate only unmasked portions of the non-layered polymeric material during the pressurizing step.

Greiner and Guruwaiya

As discussed above, Greiner fails to teach or suggest all of the recitations of independent Claim 88. Further, Guruwaiya fails to remedy the deficiencies of Greiner. Guruwaiya simply discusses the use of known masking techniques. Therefore, Greiner and Guruwaiya, alone or in any combination, fail to teach or suggest all of the recitations of independent Claim 88 and dependent claim 90 so as to provide a motivation or reasonable expectation of success that would lead one of ordinary skill in the art, at the time this invention was made, to carry out the methods of Claim 90. Accordingly, Appellants respectfully request reversal of this rejection.

C. Dependent Claim 98

Claim 98 depends from independent Claim 88 and recites wherein the non-layered polymeric material is a coating on a portion of the intraluminal prosthesis.

Greiner

As discussed above, Greiner fails to teach or suggest all of the recitations of independent Claim 88. With regard to dependent Claim 98, the Action states that the polymeric material can be formed only on the surface. The Action provides no support for this assertion and none can be found in Greiner. Greiner describes a method of impregnating a catheter, made of polymeric material, with a pharmaceutical. The catheter is immersed into a saturated solution of a pharmaceutical in a solvent. The saturated solution serves as a swelling agent and swells the polymeric material of the catheter. The catheter is contacted with the swelling agent at or near supercritical pressure and temperature of the solvent. The pressure is then reduced from supercritical pressure to release the solvent from the catheter, thereby leaving the pharmaceutical

impregnated within the catheter. Thus, there is no teaching or suggestion that the polymeric material is a coating on a portion of the intraluminal prosthesis as recited in Claim 98 of the present invention.

Accordingly, dependent Claim 98 is independently patentable over Greiner and Appellants respectfully request withdrawal of the rejection of Claim 98 over Greiner.

IV. §103 Rejection of Independent Claim 99 and Claims Dependent Thereon are Overcome

Claims 99-101 and 104 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Igaki in view of Guruwaiya. In addition, Claims 99-104 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greiner in view of Guruwaiya. Appellants respectfully request reversal of these rejections.

A. Independent Claim 99

Appellants' independent Claim 99 recites a method of impregnating an intraluminal prosthesis with a pharmacological agent, comprising:

> masking portions of an intraluminal prosthesis with a protective layer of material such that the intraluminal prosthesis has first and second unmasked portions, wherein the intraluminal prosthesis comprises non-layered polymeric material;
>
> immersing the intraluminal prosthesis in a mixture of a carrier fluid and first and second pharmacological agents;
>
> pressurizing the mixture of carrier fluid and pharmacological agents for a time sufficient to cause the carrier fluid and the first pharmacological agent to at least partially penetrate the first unmasked portion and to cause the carrier fluid and the second pharmacological agent to at least partially penetrate the second unmasked portion; and
>
> removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and such that an amount of the first pharmacological agent remains elutably trapped within the first unmasked portion in a predetermined concentration gradient and an amount of the second pharmacological agent remains elutably trapped within the second unmasked portion in a predetermined concentration gradient, wherein each concentration gradient defines an elution profile of a respective pharmacological agent from the non-layered polymeric material when the intraluminal prosthesis is deployed within a body of a subject.

Igaki, Greiner and Gurwaiya

As discussed above, Igaki fails to teach or suggest removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient. In fact, the text and data of Igaki support the conclusion that the methods of Igaki result in a polymeric material comprising a single concentration of drug. (*See,* Igaki, for example, at least, Para. 0026, 0072, 0067, Table 3, Figures 10 and 11). The only method provided by Igaki for controlling the release time point and quantity of an impregnated drug is not via a concentration gradient, but rather via the use of layers of biodegradable polymer material. Igaki specifically states "[b]y providing the layer(s) of the drug-containing biodegradable polymer in this manner, one or more drugs may be impregnated in the stent, and it is possible to permit more strict control of the drug releasing time point or the quantity of the released drug, or different drugs can be released at the desired same time point." (Igaki, Para. 0072). Igaki also describes retarding the rate of release of a drug impregnated in a stent via the use of a layer of biodegradable polymer material not containing a drug. (Igaki, Para. 0073).

One skilled in the art would not, upon reading Igaki, produce a non-layered stent with a drug concentration gradient in the stent material. To the contrary, one skilled in the art, upon reading Igaki, would use various layers to accomplish what Appellants accomplish via a concentration gradient. The fact that Igaki utilizes layers to control the time of drug release and the quantity of drug release illustrates that Igaki does not utilize or appreciate utilizing a drug concentration gradient for accomplishing time of drug release and/or quantity of drug release.

Greiner also fails to teach or suggest a drug elutably trapped within non-layered polymeric material in a predetermined concentration gradient as taught by the presently claimed invention. For at least the same reasons that Greiner fails to teach or suggest all of the recitations of independent Claim 73 and 88, as discussed above, Greiner also fails to teach or suggest all of the recitations of independent Claim 99.

The secondary reference, Guruwaiya, fails to remedy the deficiencies of primary references, Igaki and/or Greiner. The Action states that Guruwaiya teaches a method of coating

a pharmacological agent on a stent wherein certain portions of the stent are masked during the coating process. (Action, Page 3). The Action then concludes that it would have been obvious to have masked certain portions of the stent of Igaki. (Action, Page 3). The Action further states that Claim 99 is rejected under 35 U.S.C. 103(a) as being unpatenatable over Greiner in view of Guruwaiya, for substantially the same reasons as discussed for Igaki in view of Guruwaiya. Appellants respectfully disagree.

Appellants submit that to the extent that the combinations of Igaki and/or Greiner and Guruwaiya teach masking the stent of Igaki and/or Greiner, such combinations fail to teach or suggest the following recitations of independent Claim 99:

> masking portions of an intraluminal prosthesis with a protective layer of material such that the intraluminal prosthesis has first and second unmasked portions, wherein the intraluminal prosthesis comprises non-layered polymeric material;... and

> removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and such that an amount of the first pharmacological agent remains elutably trapped within the first unmasked portion in a predetermined concentration gradient and an amount of the second pharmacological agent remains elutably trapped within the second unmasked portion in a predetermined concentration gradient, wherein each concentration gradient defines an elution profile of a respective pharmacological agent from the non-layered polymeric material when the intraluminal prosthesis is deployed within a body of a subject.

Accordingly, Igaki, Greiner and Guruwaiya, alone or in combination, fail to teach or suggest all of the recitations of independent Claim 99 so as to provide a motivation or reasonable expectation of success that would lead one of ordinary skill in the art, at the time this invention was made, to carry out the methods of the claimed invention. Thus, appellants respectfully assert that the rejections under 35 U.S.C. §103 of independent Claim 99, and all claims depending therefrom, are overcome.

V. §103 Rejection of Claims 79 and 95 are Overcome

Claim 79 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Igaki in view of U.S. Patent No. 6,670,398 to Edwards (hereinafter "Edwards"). In addition, Claims 79

and 95 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greiner in view of Edwards. Appellants respectfully request reversal of these rejections.

Dependent Claims 79 and 95

Claim 79 depends from independent claim 73 and recites that the pharmacological agent comprises everolimus. Claim 95 depends from independent Claim 88 and recites that the pharmacological agent comprises everolimus.

A. Igaki and Edwards

As discussed above, Igaki fails to teach or suggest all of the recitations of independent Claim 73. Further, Edwards fails to remedy the deficiencies of Igaki. Edwards simply describes everolimus as a therapeutic drug that can be used to suppress a transplant recipient's immune response. Thus, the cited references, alone or in combination, fail to teach or suggest all of the recitations of the present invention or provide any reasonable expectation of success of achieving the present invention with such a combination. Accordingly, Appellants respectfully submit that the rejection of Claim 79 under 35 U.S.C. §103(a) over Igaki in view of Edwards is overcome and respectfully request its withdrawal.

B. Greiner and Edwards

As discussed above, Greiner fails to teach or suggest all of the recitations of the present invention. Further, Edwards fails to remedy the deficiencies of Greiner. Edwards simply describes everolimus is a therapeutic drug that can be used to suppress a transplant recipient's immune response. Thus, the cited references, alone or in combination, fail to teach or suggest all of the recitations of the present invention or provide any reasonable expectation of success of achieving the present invention with such a combination. Accordingly, Appellants respectfully submit that the rejection of Claims 79 and 95 under 35 U.S.C. §103(a) over Greiner in view of Edwards is overcome and respectfully request its withdrawal.

VI. §103 Rejections of Claims 85 and 97 are Overcome

Claims 85 and 97 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greiner in view of PCT Publication WO 01/87368 to Mehta (hereinafter "Mehta"). Appellants respectfully request reversal of these rejections.

Dependent Claims 85 and 97

Claim 85 depends from independent Claim 73 and recites the method wherein the non-layered polymeric material is non-erodible. Claim 97 depends from independent Claim 88 and recites the method wherein the non-layered polymeric material is non-erodible.

Greiner and Mehta

As discussed above, Greiner fails to teach or even suggest all of the recitations of the present invention. Further, Mehta fails to remedy the deficiencies of Greiner. Mehta simply describes deposition of a coating by altering the temperature and pressure of a SCF in which a drug or polymer to be coated is dissolved. Thus, the cited references, alone or in combination, fail to teach or suggest all of the recitations of the present invention or provide any reasonable expectation of success of achieving the present invention with such a combination. Accordingly, Appellants respectfully submit that the rejection of Claims 85 and 97 under 35 U.S.C. §103(a) over Greiner in view of Mehta is overcome and respectfully request its withdrawal.

VII. §103 Rejections of Claim 87 are Overcome

Claim 87 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Igaki in view of U.S. Patent No. 6,299,604 to Ragheb (hereinafter "Ragheb"). In addition, Claim 87 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greiner in view of Ragheb. Appellants respectfully request reversal of these rejections.

Dependent Claim 87

Claim 87 depends from independent Claim 73 and recites the method further comprising immersing the intraluminal prosthesis in a mixture of a carrier fluid and radiopaque material; and pressurizing the mixture of carrier fluid and radiopaque material for a time sufficient to cause the

carrier fluid and radiopaque material to at least partially penetrate the non-layered polymeric material.

Igaki, Greiner and Ragheb

As discussed above, Igaki and Greiner fail to teach or even suggest all of the recitations of independent Claim 73. Further, Ragheb fails to remedy the deficiencies of Igaki. Ragheb simply describes radiopaque agents as alternative bioactive materials that can be used in the vascular system. Thus, the cited references, alone or in combination, fail to teach or suggest all of the recitations of the present invention or provide any reasonable expectation of success of achieving the present invention with such a combination. Accordingly, Appellants respectfully submit that the rejections of Claim 87 under 35 U.S.C. §103(a) over Igaki in view of Ragheb and over Greiner in view of Ragheb are overcome and respectfully request their withdrawal.

VIII. §103 Rejection of Claims 81, 83, 84, 86, 93, 94, 96 and 98 is Overcome

Claims 81, 83, 84, 86, 93, 94, 96 and 98 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Greiner in view of Igaki. Appellants respectfully request reversal of these rejections.

Dependent Claims 81, 83, 84, 86, 93, 94, 96 and 98

Dependent Claim 81 recites the methods of Claims 73, 76, and 80, wherein the carbon dioxide contains one or more of a co-solvent, a surfactant, and a co-surfactant. Dependent Claim 83 recites the methods of Claims 73, 76, 80 and 81, wherein the co-solvent is selected from the group consisting of ethanol and methanol. Dependent Claim 84 recites the method of Claim 73, wherein the intraluminal prosthesis is a stent. Dependent Claim 86 recites the method of Claim 73, wherein the non-layered polymeric material is a coating on a portion of the intraluminal prosthesis. Dependent Claim 93 recites the methods of Claims 88 and 91, wherein the carbon dioxide contains one or more of a co-solvent, a surfactant, and a co-surfactant. Dependent Claim 94 recites the methods of Claims 88, 91 and 93, wherein the co-solvent is selected from the group consisting of ethanol and methanol. Dependent Claim 96 recites the method of Claim 88, wherein the intraluminal prosthesis is a stent. Dependent Claim 98 recites the method of Claim

88, wherein the non-layered polymeric material is a coating on a portion of the intraluminal prosthesis.

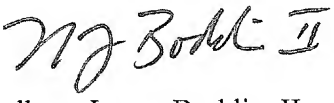
Greiner and Igaki

As discussed above, Igaki and Greiner fail to teach or suggest all of the recitations of independent Claims 73 and 88. Thus, Igaki and Greiner, alone or in combination, fail to teach or suggest all of the recitations of the present invention or provide any reasonable expectation of success with such a combination. Accordingly, Appellants respectfully submit that the rejections of dependent Claims 81, 83, 84, 86, 93, 94, 96 and 98 under 35 U.S.C. §103(a) over Igaki in view of Ragheb and over Greiner in view of Ragheb are overcome and respectfully request their withdrawal.

Conclusion

In light of the entire record and the above discussion, Appellants respectfully submit that each of the pending claims is patentable over the cited references and therefore request reversal of the rejections of Claims 73-104 and that this case be passed to issuance.

Respectfully submitted,



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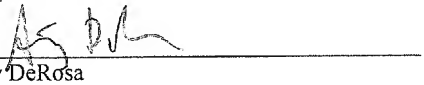

Anthony DeRosa

Claims Appendix

1-72 (Cancelled)

73. (Previously Presented) A method of impregnating an intraluminal prosthesis with a pharmacological agent, comprising:

immersing an intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent, wherein the intraluminal prosthesis comprises non-layered polymeric material;

pressurizing the mixture of carrier fluid and pharmacological agent for a time sufficient to cause the carrier fluid and pharmacological agent to at least partially penetrate the non-layered polymeric material;

removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and the pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient, wherein the concentration gradient defines an elution profile of the pharmacological agent from the non-layered polymeric material when the intraluminal prosthesis is deployed within a body of a subject.

74. (Previously Presented) The method of Claim 73, wherein the step of removing pressure is carried out under controlled conditions in which at least one parameter selected from the group consisting of temperature, rate of temperature change, pressure, rate of pressure change, carrier fluid quantity, and rate of carrier fluid quantity, is controlled in a predetermined pattern.

75. (Previously Presented) The method of Claim 73, further comprising masking one or more portions of the intraluminal prosthesis with a protective layer of material prior to immersing the intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent, wherein the protective layer of material is configured such that the mixture of carrier fluid and

pharmacological agent at least partially penetrate only unmasked portions of the non-layered polymeric material during the pressurizing step.

76. (Previously Presented) The method of Claim 73, wherein the carrier fluid is carbon dioxide.

77. (Previously Presented) The method of Claim 73, wherein the carrier fluid is carbon dioxide and wherein the step of pressurizing the mixture of carrier fluid and pharmacological agent is performed using an inert second gas.

78. (Previously Presented) The method of Claim 77, wherein the second gas is selected from the group consisting of helium, nitrogen, and argon.

79. (Previously Presented) The method of Claim 73, wherein the pharmacological agent comprises everolimus.

80. (Previously Presented) The method of Claim 76, wherein the carbon dioxide is present in a supercritical state.

81. (Previously Presented) The method of Claim 80, wherein the carbon dioxide contains one or more of a co-solvent, a surfactant, and a co-surfactant.

82. (Previously Presented) The method of Claim 73, wherein the carrier fluid is configured to alter diffusion coefficients of the non-layered polymeric material.

83. (Previously Presented) The method of Claim 81, wherein the co-solvent is selected from the group consisting of ethanol and methanol.

84. (Previously Presented) The method of Claim 73, wherein the intraluminal prosthesis is a stent.

85. (Previously Presented) The method of Claim 73, wherein the non-layered polymeric material is non-erodible.

86. (Previously Presented) The method of Claim 73, wherein the non-layered polymeric material is a coating on a portion of the intraluminal prosthesis.

87. (Previously Presented) The method of Claim 73, further comprising:

immersing the intraluminal prosthesis in a mixture of a carrier fluid and radiopaque material; and

pressurizing the mixture of carrier fluid and radiopaque material for a time sufficient to cause the carrier fluid and radiopaque material to at least partially penetrate the non-layered polymeric material.

88. (Previously Presented) A method of impregnating an intraluminal prosthesis with a pharmacological agent, comprising:

immersing an intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent, wherein the intraluminal prosthesis comprises non-layered polymeric material;

placing the intraluminal prosthesis within a pressure vessel;

pressurizing the interior of the pressure vessel with an inert gas to a predetermined pressure, wherein the inert gas is selected from the group consisting of helium, nitrogen, and argon;

supplying a mixture of a carrier fluid and a pharmacological agent into the pressure vessel;

exposing the non-layered polymeric material and the mixture of carrier fluid and pharmacological agent in the pressure vessel for a time such that the carrier fluid and pharmacological agent at least partially penetrate the non-layered polymeric material; and

releasing the pressure in the pressure vessel over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric

material and the pharmacological agent becomes elutably trapped within the non-layered polymeric material in a predetermined concentration gradient, wherein the concentration gradient defines an elution profile of the pharmacological agent from the non-layered polymeric material when the intraluminal prosthesis is deployed within a body of a subject.

89. (Previously Presented) The method of Claim 88, wherein the step of releasing pressure is carried out under controlled conditions in which at least one parameter selected from the group consisting of temperature, rate of temperature change, pressure, rate of pressure change, carrier fluid quantity, and rate of carrier fluid quantity, is controlled in a predetermined pattern.

90. (Previously Presented) The method of Claim 88, further comprising masking one or more portions of the intraluminal prosthesis with a protective layer of material prior to immersing the intraluminal prosthesis in a mixture of a carrier fluid and a pharmacological agent, wherein the protective layer of material is configured such that the mixture of carrier fluid and pharmacological agent at least partially penetrate only unmasked portions of the non-layered polymeric material during the pressurizing step.

91. (Previously Presented) The method of Claim 88, wherein the carrier fluid is carbon dioxide.

92. (Previously Presented) The method of Claim 91, wherein the carbon dioxide is in a supercritical state.

93. (Previously Presented) The method of Claim 91, wherein the carbon dioxide contains one or more of a co-solvent, a surfactant, and a co-surfactant.

94. (Previously Presented) The method of Claim 93, wherein the co-solvent is selected from the group consisting of ethanol and methanol.

95. (Previously Presented) The method of Claim 88, wherein the pharmacological agent is everolimus.

96. (Previously Presented) The method of Claim 88, wherein the intraluminal prosthesis is a stent.

97. (Previously Presented) The method of Claim 88, wherein the non-layered polymeric material is non-erodible.

98. (Previously Presented) The method of Claim 88, wherein the non-layered polymeric material is a coating on a portion of the intraluminal prosthesis.

99. (Previously Presented) A method of impregnating an intraluminal prosthesis with a pharmacological agent, comprising:

masking portions of an intraluminal prosthesis with a protective layer of material such that the intraluminal prosthesis has first and second unmasked portions, wherein the intraluminal prosthesis comprises non-layered polymeric material;

immersing the intraluminal prosthesis in a mixture of a carrier fluid and first and second pharmacological agents;

pressurizing the mixture of carrier fluid and pharmacological agents for a time sufficient to cause the carrier fluid and the first pharmacological agent to at least partially penetrate the first unmasked portion and to cause the carrier fluid and the second pharmacological agent to at least partially penetrate the second unmasked portion; and

removing the pressure over a predetermined period of time and under controlled conditions such that the carrier fluid diffuses out of the non-layered polymeric material and such that an amount of the first pharmacological agent remains elutably trapped within the first unmasked portion in a predetermined concentration gradient and an amount of the second pharmacological agent remains elutably trapped within the second unmasked portion in a predetermined concentration gradient, wherein each concentration gradient defines an elution

profile of a respective pharmacological agent from the non-layered polymeric material when the intraluminal prosthesis is deployed within a body of a subject.

100. (Previously Presented) The method of Claim 99, wherein the step of removing pressure is carried out under controlled conditions in which at least one parameter selected from the group consisting of temperature, rate of temperature change, pressure, rate of pressure change, carrier fluid quantity, and rate of carrier fluid quantity, is controlled in a predetermined pattern.

101. (Previously Presented) The method of Claim 99, wherein the carrier fluid is carbon dioxide.

102. (Previously Presented) The method of Claim 99, wherein the carrier fluid is carbon dioxide and wherein the step of pressurizing the mixture of carrier fluid and pharmacological agent is performed using an inert second gas.

103. (Previously Presented) The method of Claim 102, wherein the second gas is selected from the group consisting of helium, nitrogen, and argon.

104. (Previously Presented) The method of Claim 101, wherein the carbon dioxide is present in a supercritical state.

Evidence Appendix

Evidence listing:

Concentration definitions from:

- Biology-Online.org
- Merriam Webster Online Dictionary
- Online Medical Dictionary
- Answers.com

These documents were submitted concurrently with the response dated April 18, 2008.

Related Proceedings Appendix

NONE

Concentration Gradient

concentration gradient

noun

1. a gradual change in the concentration of solutes in a solution as a function of distance through a solution.
2. the gradual difference in the concentration of solutes in a solution between two regions. In biology, a gradient results from an unequal distribution of ions across the cell membrane. When this happens, solutes move along a concentration gradient. This kind of movement is called *diffusion.*

*"The movement of solutes along a concentration gradient is common in many biological processes. For a more elaborated discussion, read the **Tutorial in Cell Biology** where various ways substances pass through a cell membrane are described.*

Please contribute to this project, if you have more information about this term feel free to edit this page

Gradient

Gradient

(Science: physics) mathematical term for the operator which determines the magnitude and direction of the greatest rate-of-change of a given function with position. Similarly used to describe such a rate-of-change.

For instance, at a given point on a hill, the slope of the hill in the steepest uphill direction is the gradient of the altitude function for the hill.

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gradient

One entry found.

gradient

Main Entry: **gra·di·ent**
Pronunciation: \'grā-dē-ənt\
Function: *noun*
Etymology: Latin *gradient-, gradiens,* present participle of *gradi*
Date: 1835

1 a : the rate of regular or graded ascent or descent : INCLINATION **b :** a part sloping upward or downward
2 : change in the value of a quantity (as temperature, pressure, or concentration) with change in a given variable and especially per unit distance in a specified direction
3 : the vector sum of the partial derivatives with respect to the three coordinate variables *x, y,* and *z* of a scalar quantity whose value varies from point to point
4 : a graded difference in physiological activity along an axis (as of the body or an embryonic field)
5 : change in response with distance from the stimulus

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Pronunciation Symbols

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Browse words next to:
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A B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

gradient Go

gradient

<physics> Mathematical term for the operator which determines the magnitude and direction of the greatest rate-of-change of a given function with position. Similarly used to describe such a rate-of-change.

For instance, at a given point on a hill, the slope of the hill in the steepest uphill direction is the gradient of the altitude function for the hill.

(09 Oct 1997)

Previous: grade III astrocytoma, grade IV astrocytoma, Gradenigo, Giuseppe, Gradenigo's syndrome
Next: gradient elution, gradient encoding, gradient perception, grading

Dictionary:

concentration gradient

n.

The graduated difference in concentration of a solute per unit distance through a solution.

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How do you find small business connections in Raleigh?
Join Slingshot's online small business community to find other local merchants in your industry. www.joinslingshot.com

Is there an online small business community in my area?
Join Slingshot's online to network, to seek advice, and to find support from other small business owners. www.joinslingshot.com

Wikipedia: electrochemical gradient

In cellular biology, an **electrochemical gradient** refers to the electrical and chemical properties across a membrane. These are often due to *ion gradients*, particularly *proton gradients*, and can represent a type of potential energy available for work in a cell. This can be calculated as a thermodynamic measure termed electrochemical potential that combines the concepts of energy stored in the form of chemical potential which accounts for an ion's *concentration gradient* across a cellular membrane and electrostatics which accounts for an ion's tendency to move relative to the membrane potential.

Overview

Electrochemical potential is important in electroanalytical chemistry and industrial applications such as batteries and fuel cells. It represents one of the many interchangeable forms of potential energy through which energy may be conserved.

In biological processes the direction an ion will move by diffusion or active transport across membrane is determined by the electrochemical gradient. In mitochondria and chloroplasts, proton gradients are used to generate a **chemiosmotic potential** that is also known as a **proton motive force**. This potential energy is used for the synthesis of ATP by oxidative phosphorylation.

An electrochemical gradient has two components. First, the electrical component is caused by a charge difference across the lipid membrane. Second, a chemical component is caused by a differential concentration of ions across the membrane. The combination of these two factors determines the thermodynamically favourable direction for an ion's movement across a membrane.

Electrochemical gradients are analogous to hydroelectric dams and equivalent to the water pressure across the dam. Membrane transport proteins such as the sodium-potassium pump within the membrane are equivalent to turbines that convert the waters potential energy to other forms of physical or chemical energy, and the ions that pass through the membrane are equivalent to water that is now found at the bottom of the dam. Alternatively, energy can be used to pump water up into the lake above the dam. Similarly chemical energy in cells can be used to create electrochemical gradients.

Chemistry

The term is typically applied in contexts where a chemical reaction is to take place, such as one involving the transfer of an electron at a battery electrode. In a battery, an electrochemical potential arising from the movement of ions balances the reaction energy of the electrodes. The maximum voltage that a battery reaction can produce is sometimes called the standard electrochemical potential of that reaction (see also electrode potential and Table of standard electrode potentials). In instances pertaining specifically to the movement of electrically charged solutes, the potential is often expressed in units of volts. See: Concentration cell

Biological context

In biology, the term is sometimes used in the context of a chemical reaction, in particular to describe the energy source for the chemical synthesis of ATP. More generally, however, it is used to characterize the inclined tendency of solutes to simply diffuse across a membrane, a process involving no chemical transformation.

Ion gradients

With respect to a cell, organelle, or other subcellular compartments, the inclined tendency of an electrically charged solute, such as a potassium ion, to move across the membrane is decided by the difference in its electrochemical potential on either side of the membrane, which arises from three factors:

- the difference in the concentration of the solute between the two sides of the membrane
- the charge or "valence" of the solute molecule
- the difference in voltage between the two sides of the membrane (i.e. the transmembrane potential).

A solute's electrochemical potential difference is zero at its "reversal potential". The transmembrane voltage to which the solute's net flow across the membrane is also zero. This potential is predicted theoretically either by the Nernst equation (for systems of one permeant ion species) or the Goldman-Hodgkin-Katz equation (for more than one permeant ion species). Electrochemical potential is measured in the laboratory and field using reference electrodes.

Transmembrane ATPases or transmembrane proteins with ATPase domains are often used for making and utilizing ion gradients. The enzyme Na+/K+ ATPase use ATP to make a sodium ion gradient and a potassium ion gradient. The electrochemical potential is used as energy storage, chemiosmotic coupling is one of several ways a thermodynamically unfavorable reaction can be driven by a thermodynamically favorable one. Cotransport of ions by symporters and antiporter carriers are common to actively move ions across biological membranes.

Proton gradients

The **proton gradient** can be used as an intermediate energy storage for heat production and flagellar rotation. Additionally, it is an interconvertible form of energy in active transport, electron potential generation, NADPH synthesis, and ATP synthesis/hydrolysis.

The **electrochemical potential** difference between the two sides of the membrane in mitochondria, chloroplasts, bacteria and other membranous compartments that engage in active transport involving proton pumps, is at times called a **chemiosmotic potential** or **proton motive force** (see chemiosmosis). In this context, protons are often considered separately using units either of concentration or pH.

Proton Motive Force: two protons are expelled at each coupling site, generating the Proton Motive Force. ATP is made indirectly using the PMF as a source of energy. Each pair of protons yields one ATP.

Some archaea, most notably halobacteria, make proton gradients by pumping in protons from the environment with the help of the solar driven enzyme bacteriorhodopsin, here it is used for driving the molecular motor enzyme ATP synthase to make the necessary conformational changes required to synthesize ATP.

Proton gradients are also made by bacteria by running ATP synthase in reverse; this is used to drive flagella.

The F_1F_0 ATP synthase is a reversible enzyme. Large enough quantities of ATP cause it to create a transmembrane proton gradient. This is used by fermenting bacteria - which do not have an electron transport chain, and hydrolyze ATP to make a proton gradient - which they use for flagella and the transportation of nutrients into the cell.

In respiring bacteria under physiological conditions. ATP synthase generally runs in the opposite direction creating ATP while using the proton motive force created by the electron transport chain as a source of energy. The overall process of creating energy in this fashion is termed: oxidative phosphorylation. The same process takes place in mitochondria where ATP synthase is located in the inner mitochondrial membrane, so that F_1-part sticks into mitochondrial matrix, where ATP synthesis takes place.

References

- Campbell, Reece (2005). *Biology*. Pearson Benjamin Cummings. ISBN 0-8053-7146-X.
- [1]

External links

See also

- Concentration cell
- Transmembrane potential difference
- Action potential
- Cell potential
- Electrodiffusion
- Galvanic cell
- Electrochemical cell